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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Pharmaceutical compositions containing a therapeutically active agent, a diffusion barrier coating and coating comprising a hydrophobic material.

PHARMACEUTICAL COMPOSITIONS

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PHARMACEUTICAL COMPOSITIONS

[0001] This application claims priority from U.S. Provisional Application No. 60/403,711, filed August 15, 2002, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmaceutical substrate compositions comprising a therapeutically active agent, a diffusion barrier coating comprising an anionic polymer and a coating comprising a hydrophobic material coated over said diffusion barrier coating.

BACKGROUND OF THE INVENTION

[0003] It is known in the pharmaceutical art to prepare compositions which provide for controlled release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Controlled release formulations known in the art include specially coated pellets, coated tablets and capsules, and ion exchange resins, wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some controlled release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

[0004] One of the requirements for an acceptable pharmaceutical composition is that it must be stable, so as not to exhibit substantial decomposition of the active ingredient during the time between manufacture of the composition and use by the patient.

[0005] In certain instances, it has been found that certain active ingredients may tend to leak or seep through the coatings of certain dosage forms during the manufacturing

process which may result in the immediate release of the active agent upon administration when a controlled release of the active agent is desired. Additionally, in certain instances, the leak or seepage of the active agent may result in the substantial release of the active agent where no or substantially no release of the active agent is desired.

[0006] There exists a need in the art to develop controlled release pharmaceutical formulations wherein the active ingredient in the formulation does not migrate through the controlled release coating during the manufacturing process and/or upon storage prior to administration of the formulation.

OBJECTS AND SUMMARY OF THE INVENTION

[0007] It is an object of the present invention to provide an oral controlled release pharmaceutical formulation having an improved stability of the therapeutic agent in the formulation by the inclusion of an anionic polymer in the formulation.

[0008] It is a further object of certain embodiments of the present invention to provide an oral controlled release pharmaceutical formulation having decreased migration of therapeutic agent through the controlled release coating during the manufacturing process and/or upon storage prior to administration of the formulation.

[0009] It is a further object of certain embodiments of the present invention to provide an oral pharmaceutical formulation comprising a substrate having a therapeutic agent, a diffusion barrier coating comprising an anionic polymer coated over the substrate, and a coating comprising a hydrophobic material coated over the diffusion barrier coating.

[0010] These objects and others are accomplished by the present invention, which is directed in part to a pharmaceutical formulation comprising a therapeutic agent, a diffusion barrier coating, and a coating comprising a hydrophobic material.

[0011] In certain embodiments, the present invention is directed to a substrate formulation comprising one or more pharmaceutically acceptable substrates comprising a therapeutic agent, a diffusion barrier coating comprising an anionic polymer and coated onto the substrate, and a coating comprising a hydrophobic material and coated over the diffusion barrier coating.

[0012] In certain preferred embodiments, the pharmaceutical formulation comprises a pharmaceutically acceptable inert bead formulation coated with a layer comprising a therapeutic agent; which is overcoated with a diffusion barrier coating comprising an anionic polymer; and further overcoated with a coating comprising a hydrophobic material.

[0013] In certain embodiments, the coating comprising the hydrophobic material provides for the controlled released of the therapeutic agent.

[0014] In certain embodiments, the coating comprising the hydrophobic material provides for the sequestration of the therapeutic agent.

[0015] In certain preferred embodiments, the therapeutic agent is a protonated drug, e.g., a drug which is positively charged.

[0016] In certain embodiments, the pharmaceutical formulation of the present invention comprises a substrate comprising an opioid antagonist, a diffusion barrier coating comprising an anionic polymer coated over the substrate, and a coating comprising a hydrophobic material coated over said diffusion barrier coating.

[0017] In certain embodiments, the pharmaceutical formulation of the present invention comprises a substrate comprising an opioid analgesic, a diffusion barrier coating comprising an anionic polymer coated over the substrate, and a coating comprising a hydrophobic material coated over said diffusion barrier that provides for the controlled release of the opioid analgesic.

[0018] For purposes of the present invention, the term "controlled release" means that the therapeutic agent is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the agent are maintained over an extended period of time, e.g., providing an 8 to 24 hour therapeutic effect.

[0019] For purposes of the present invention, the term "sequestered" means the therapeutic agent is not released or not substantially released when the dosage form is administered intact. For example, PCT Publication No. WO 01/58451, the disclosure of which is hereby incorporated by reference in its entirety, discloses an oral dosage form comprising a sequestered opioid antagonist which is not released or substantially not released when the dosage form is administered intact.

DETAILED DESCRIPTION

[0020] The present invention is directed to improving the stability of an oral controlled release pharmaceutical formulation comprising a therapeutic agent by the inclusion of an anionic polymer in the formulation. The formulation of the present invention preferably has three components. The first component is a substrate which comprises one or more therapeutic agents. The therapeutic agent is preferably coated onto the substrate. The second component is an anionic polymer layer, which is coated onto the substrate comprising the therapeutic agent (e.g., coated over the therapeutic agent). The third component is a coating comprising a hydrophobic material and is coated over the second component. The third component may provide for the controlled release of the therapeutic agent or alternatively may provide for the sequestration of the therapeutic agent. Preferably the therapeutic agent is a protonated drug molecule (e.g., positively charged) and the anionic polymer of the second component, having an affinity for the protonated drug molecule binds with and prevents the diffusion of the therapeutic agent

through the hydrophobic coating of the formulation during the manufacturing process and/or upon storage prior to administration. The diffusion of the agent through the hydrophobic coating is especially problematic during the manufacturing process when the hydrophobic material is applied to the substrate as an aqueous dispersion. Accordingly, the diffusion barrier coating is useful in such embodiments to prevent or reduce the migration during the application of the aqueous dispersion of hydrophobic material.

[0021] Therapeutic agents for use in the formulations of the present invention are preferably protonated drugs (e.g., positively charged) that have affinity for the anionic polymer in the anionic polymer layer. In certain embodiments, the therapeutic agent of the present invention is a narcotic antagonist (e.g., naltrexone, naloxone, nalorphone) and/or an opiate analgesic (e.g., anileridine, buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, morphine, meperidine, oxycodone, oxymorphone, tramadol). In certain alternative embodiments, the therapeutic agent can be selcted from, e.g., cardiovascular drugs (e.g., acebutolol, amiodarone, clonidine, enalapril, guanfacine, hydralazine, mecamylamine, nicardipine, nifenalol, procainamide, quinidine, sotalol, verapamil), antihistamines (e.g., antazoline, bromopheniramine, carbinoxamine, cetirizine, chlorpheniramine, clemastine, diphenhydramine, doxylamine, promethazine), respiratory drugs (e.g., dextromethorphan, pseudoephedrine, albuterol), CNS stimulants (e.g., amphetamine, caffeine methylphenidate, sibutramine), antiviral/antibacterial/antimalarial drugs (e.g, amantadine, amikacin, amodiaquine, bacampicillin, chloroquine, primaquine, quinine), antidepressants (e.g, acepromazine, amitriptyline, bupropion, desipramine, doxepin, fluoxetine, imipramine, nefazodone, nortriptyline, phenelzine, protriptyline, sertraline, trazodone, trimipramine, venlafaxine), anesthetics (e.g, bupivacaine, chloroprocaine, lidocaine, mepivacaine, prilocaine, procaine, tetracaine), CNS depressants (buspirone, chlordiazepoxide, flurazepam, hydroxyzine, midazolam, zolpidem), , mixtures thereof, salts thereof, and the like. In certain embodiments, the agent comprises an opioid antagonist. In certain embodiments, the agent comprises both an opioid analgesic and an opioid antagonist. In other embodiments, the therapeutic agent comprises an opioid analgesic and does not comprise

an opioid antagonist. In preferred embodiments, the drug molecule is in the form of the acidic salt of the drug molecule.

[0022] Preferably the therapeutic agent is applied to the substrate. The substrates coated with the therapeutic agent may be prepared, e.g., by dissolving the therapeutic agent in a solvent such as water and then spraying the solution onto the substrates, e.g., nu pariel 18/20 beads. A preferred method of applying the therapeutic agent to the substrate is through the use of a polymer film. An example of a polymer film for use in the present invention includes for example and without limitation, hydroxypropylmethylcellulose, ethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, ethylcellulose, mixtures thereof, and the like. The polymer may be dissolved or dispersed in an aqueous or organic medium with the therapeutic agent and coated onto the substrates. In addition to the therapeutic agent, the polymer film may contain optional fillers, pigments, and dyes known in the art.

[0023] Conventional coating techniques such as spray or pan coating, as described hereinafter, may be employed to apply the coating comprising the therapeutic agent to the substrate. The amount of the therapeutic agent applied to the substrate may vary depending upon the concentration desired in the finished product. Preferably the amount of the weight of the applied film including the therapeutic agent on the substrate is from about 1 to about 50% weight gain, more preferably from about 2 to about 30 % weight gain.

[0024] Substrates for use in the present invention include, for example and without limitation, beads, microspheres, seeds, pellets, ion-exchange resin beads, other multi-particulate systems, and the like. Preferably the substrates of the present invention are pharmaceutically acceptable inert beads. The beads are typically made from one or a mixture of a group selected from but not limited to sucrose, mannitol, lactose, dextrose, sorbitol, cellulose, starch, mixtures thereof, and the like. The preferred size of the inert beads is in the range of from 0.1 mm to about 2.5 mm. The inert beads are preferably pre-manufactured beads known in the art (e.g., non-pareil PG beads). In certain

embodiments, the substrates for use in the present invention may include a matrix multiparticulate system, which may comprise the therapeutic agent in a plurality of immediate release matrices, or a compressed matrix formulation (e.g., matrix tablet) comprising the therapeutic agent in an immediate or controlled release matrix.

[0025] In accordance with the present invention, the substrates comprising the therapeutic agent, are then overcoated with the diffusion barrier coating. In a preferred embodiment, wherein the substrate is a bead, the formulation comprises a plurality of beads coated with the therapeutic agent which are then overcoated with a diffusion barrier coating.

[0026] The diffusion barrier coating preferably comprises an anionic polymer and optionally other excipients. Examples of anionic polymers for use in the present invention include for example and without limitation, acrylic acid polymers and copolymers, methacrylic acid polymers and copolymers, non-acrylic enteric coating polymers, mixtures thereof, and the like. Also useful in accordance with the present invention in place of, or in addition to, the anionic polymer are cellulose derivatives (e.g., carboxymethylcellulose), starches (carboxymethyl starch), gums (xanthan gum), mixtures thereof, and the like, which have affinity for the protonated therapeutic agent included in the formulation.

[0027] Examples of acrylic acid polymers and copolymers, and methacrylic acid polymers and copolymers include, for example and without limitation, carboxypolymethylene, poly(acrylic acid), polyacrylamide, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0028] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well

known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0029] Certain methacrylic acid ester-type polymers of a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc may also be useful for purposes of the present invention. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH < 5.7 and is soluble at about pH > 6. Eudragit® S does not swell at about pH < 6.5 and is soluble at about pH > 7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

[0030] In certain embodiments, the diffusion barrier coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000.

[0031] Certain non-acrylic enteric coating polymers for use in the diffusion barrier coating of the present invention include, for example and without limitation, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellatate, cellulose acetophthalate, cellulose acetate terephthalate, polyvinyl alcohol phthalate, mixtures thereof, and the like.

[0032] Other optional ingredients can be included in the diffusion barrier coating, such as for example, plasticizers, binders, lubricants, glidants, fillers, etc, described hereinafter. In certain preferred embodiments, the diffusion barrier coating includes a plasticizer as described hereinafter.

[0033] The diffusion barrier coating can be applied onto the substrates comprising the therapeutic agent in an amount of from about 0.1 to about 20% by weight, preferably from about 1 to about 10 % by weight of the substrates comprising the therapeutic agent. As with the application of the therapeutic agent to the substrates, the diffusion barrier coating may be applied by spraying a suitable solution or dispersion comprising the anionic polymer employing a suitable mixture of solvents and using techniques known in the art. The diffusion barrier coating preferably prevents or decreases the amount of migration of the therapeutic agent from the dosage form by having an affinity for the protonated therapeutic agent of the substrate.

[0034] After the substrates comprising the therapeutic agent are coated with the diffusion barrier coating, they are then overcoated with a coating comprising a hydrophobic material. Preferably the hydrophobic material provides for the controlled release of the therapeutic agent, or the sequestration of the therapeutic agent.

[0035] Certain hydrophobic materials for inclusion in the coating include, for example and without limitation, cellulosic materials and polymers, acrylic polymers, mixtures thereof, and the like.

[0036] In certain embodiments the hydrophobic material comprises a cellulosic material or cellulosic polymers, including alkylcelluloses. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of the hydrophobic coating according to the invention.

[0037] One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

[0038] Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

[0039] In certain embodiments the hydrophobic material comprises a pharmaceutically acceptable acrylic polymer as desired above, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0040] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

[0041] Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc. As described above, there are several different types of Eudragit®.

[0042] In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D as described above. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

[0043] The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a controlled release formulation having a desirable dissolution profile. Desirable controlled release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

[0044] In certain embodiments, wherein the coating comprises an aqueous dispersion of a hydrophobic material such as for example an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the controlled release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing controlled release coating before using the same as a coating material. Generally, the amount of plasticizer

is included in a coating solution in an amount of from about 1 to about 50 percent by weight of the hydrophobic material. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

[0045] Examples of suitable plasticizers for ethylcellulose include, but are not limited to, water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used.

[0046] Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for use in the present invention.

[0047] In certain embodiments where an aqueous dispersion of a hydrophobic polymer such as an alkylcellulose is applied to the substrate, the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60° C and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Patent Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

[0048] In formulations where a controlled release coating comprising an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the controlled release coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the controlled release coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45° C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Patent Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

[0049] The controlled release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, combinations thereof, and the like.

[0050] The coating solutions of the present invention preferably contain, in addition to the plasticizer and solvent system (e.g., water), a colorant to provide elegance and product distinction. Color may be added, for example, to the aqueous dispersion of hydrophobic material. For example, color may be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to the water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retardant effect of the controlled release coating.

[0051] The plasticized aqueous dispersion (e.g., solution or suspension) of hydrophobic material may be applied onto the substrate comprising the therapeutic agent by spraying using any suitable spray equipment known in the art. The dispersion may be applied to the diffusion barrier coated substrates comprising the therapeutic agent in a conventional coating pan or, alternatively, using an automated system such as a CF granulator, for example a FREUND CF granulator, a GLATT fluidized bed processor, an AEROMATIC, a modified ACCELA-COTA or any other suitably automated bead coating equipment.

[0052] Preferably 2-25 ml of the solution/suspension is applied per coat per kilogram of substrate. In an automated system the total amount of solution/suspension applied to the substrate is the same as that applied in a conventional coating pan, except that the solution/suspension is applied continuously.

[0053] Preferably, when a coating pan is used the coating is applied at a rate of 20-30 coats between each drying step until all of the coats have been applied. Between applications the substrates may be dried for more than 12 hours at a temperature of 50°C = 60°C., most suitably 55°C.

[0054] In an automated coating system the rate of application of solution/suspension may be 0.5-10 g/kg of substrate/min.

[0055] In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the substrate and effects drying while the acrylic polymer coating is sprayed on. In certain embodiments, a sufficient amount of the aqueous dispersion of hydrophobic material is applied to the diffusion barrier coated substrate comprising the therapeutic agent to obtain a predetermined controlled release of the therapeutic agent (i.e., drug) when the coated substrate is exposed to aqueous solutions, e.g., gastric fluid.

[0056] In certain embodiments a further overcoat of a film-former, such as Opadry®, is optionally applied to the substrates after coating the substrates with the hydrophobic coating. This overcoat is provided, if at all, preferably in order to substantially reduce agglomeration of the beads.

[0057] After the diffusion barrier coated substrates (e.g., beads) are overcoated with the hydrophobic coating, the overcoated substrates (e.g., controlled release beads) which are formed may be filled into hard or soft gelatin capsules. Alternatively, the overcoated substrates may be compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as, for example and without limitation, microcrystalline cellulose sold under the Trade Mark "AVICEL" or a co-crystallised powder of highly modified dextrins (3% by weight) and sucrose sold under the Trade Mark "DI-PAC" in such a way that the specific dissolution rate of the controlled release substrates (e.g., beads) is maintained.

[0058] Following the formation of the mixture into a tablet, it may be desirable to apply a very thin coating to the external surface of the tablet. The function of the coating, when applied, is to enhance the intactness of the tablet. The coating may comprise a polymer, such as polyvinyl alcohol or a polyvinylpyrrolidol, which, maintains the tablet intact but does not inhibit the capillary uptake by the tablet once placed in the aqueous environment of use (e.g., gastrointestinal system), although dissolution time may be slightly increased when a coating is applied to the tablet.

[0059] In certain embodiments, the formulations of the present invention may further include a lubricant which may be mixed with any of the coatings prior to application. Suitable lubricants include for example talc, magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate, mixtures thereof and the like. Generally, when a lubricant is present, the quantity of lubricant will be from about 0.1% to about 10%, preferably about 0.1% to about 5%.

[0060] In certain embodiments, the formulations of the present invention may further include a binder. The binder may be any pharmaceutically acceptable binder known to those skilled in the art. Such binders include, for example, polyvinylpyrrolidone, natural and synthetic gums including gum arabic, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, pullulan, dextrin, starch, mixtures thereof and the like. The binder may be mixed with any of the coatings prior to application or may be dissolved or dispersed in an aqueous or organic solution, or a mixture thereof. Aqueous binder solutions or dispersions are especially preferred. Suitable binding agents which are generally considered to be water-soluble include polyvinylpyrrolidone, hydroxypropylmethylcellulose, and maize starch. Many other water-soluble binding agents which would be suitable for use in conjunction with the present invention are known to those skilled in the art.

[0061] In certain embodiments, the compositions of the present invention further comprise a pharmaceutically acceptable carrier. Generally, the carriers to be used herein are, for example and without limitation, microcrystalline cellulose, polyvinylpyrrolidone, lactose, dextrose, sucrose, starch, sorbitol, mannitol, mixtures thereof, and the like. Other examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

[0062] Other optional ingredients that can be included in the formulations of the present invention include glidants such as talc, titanium dioxide, magnesium stearate, silicon dioxide, dibutyl sebacate, ammonium hydroxide, oleic acid colloidal silica, mixtures thereof and the like, which may be mixed with any of the coatings prior to application, and/or dissolved or dispersed in an aqueous and/or organic solvent prior to application.

[0063] In certain embodiments, the formulations of the present invention further include a release-modifying agent. The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or

leached from the controlled release coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose. In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

[0064] The controlled release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

[0065] The controlled release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

[0066] The controlled release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

[0067] In certain embodiments it may be necessary to include a stabilizer in the formulation of the present invention to prevent the degradation of the therapeutic agent. For example, a degradation product of naltrexone hydrochloride includes for example and without limitation, 10-hydroxynaltrexone; 10-ketonaltrexone; 2,2' bisnaltrexone (pseudonaltrexone); oxides of 2,2' bisnaltrexone; dioxides of 2,2' bisnaltrexone; aldol adduct of naltrexone and 10-hydroxynaltrexone; aldol adduct of naltrexone and 10-ketonaltrexone; naltrexone-N-oxide; 10-hydroxynaltrexone-N-oxide; 10-ketonaltrexone-N-oxide; semiquinones of naltrexone; free radical peroxides of naltrexone; aldol adduct of naltrexone; aldol adducts of naltrexone coupled at the 7,6 position; aldol adducts of naltrexone coupled at the 6,5 position; ether-linked adduct of naltrexone; ether-linked adduct of naltrexone and 10-hydroxynaltrexone; ether-linked adduct of naltrexone and

10-ketonaltrexone; dehydrogenated naltrexone; hydroxy-naltrexone; keto-naltrexone; salts thereof and mixtures thereof; and the like.

[0068] Stabilizers of use in this invention for preventing the degradation of, e.g., naltrexone hydrochloride, include for example and without limitation, organic acids, carboxylic acids, acid salts of amino acids (e.g., cysteine, L-cysteine, cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride), sodium metabisulphite, ascorbic acid and its derivatives, malic acid, isoascorbic acid, citric acid, tartaric acid, palmitic acid, sodium carbonate, sodium hydrogen carbonate, calcium carbonate, calcium hydrogen phosphate, sulphur dioxide, sodium sulphite, sodium bisulphate, tocopherol, as well as its water- and fat-soluble derivatives, such as e.g., tocofersolan or tocopherol acetate, sulphites, bisulphites and hydrogen sulphites or alkali metal, alkaline earth metal and other metals, PHB esters, gallates, butylated hydroxyanisol (BHA) or butylated hydroxytoluene (BHT), and 2,6-di-t-butyl-.alpha.-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene, butylhydroxyanisole, pyrocatechol, pyrogallol, propyl/gallate, and nordihydroguaiaretic acid, as well as lower fatty acids, fruit acids, phosphoric acids, sorbic and benzoic acids as well as their salts, esters, derivatives and isomeric compounds, ascorbyl palmitate, lecithins, mono- and polyhydroxylated benzene derivatives, ethylenediamine-tetraacetic acid and its salts, citraconic acid, conidendrine, diethyl carbonate, methylenedioxyphenols, kephalines, β,β'-dithiopropionic acid, biphenyl and other phenyl derivatives, pharmaceutically acceptable salts thereof, and mixtures thereof. In certain preferred embodiments, the stabilizer is BHT. In other preferred embodiments, the stabilizer is ascorbic acid. All or part of the ascorbic acid can be replaced with a metal or ammonium ascorbate, e.g., sodium, potassium and/or iodine ascorbate(s). Sodium ascorbate is preferred.

[0069] In addition to the above ingredients, the compositions of the present invention may also contain suitable quantities of other materials, e.g., granulating aids, colorants, and flavorants that are conventional in the pharmaceutical art. The quantities of these

additional materials will be sufficient to provide the desired effect to the desired composition.

[0070] In certain embodiments of the present invention, the therapeutic agent may also be included in immediate release coating in the formulation. The immediate release coating of the therapeutic agent is included in an amount which is effective to reduce the time to maximum concentration of the therapeutic agent in the blood (e.g., plasma). In certain embodiments, the immediate release layer is coated over the controlled release coating. On the other hand, the immediate release layer may be coated over the surface of tablets or capsules of the final formulation. One skilled in the art would recognize still other alternative manners of incorporating an immediate release form of the therapeutic agent into the formulation. In certain alternate embodiments an immediate release layer comprising a different therapeutic agent other than the therapeutic agent of the controlled release substrate may be coated over the control release coating comprising the hydrophobic polymer.

[0071] In certain embodiments, the present invention is further directed to a process for the preparation of the oral pharmaceutical formulations described herein. Said process preferably comprises the steps of

a. forming a substrate comprising a therapeutic agent or mixture of therapeutic agents optionally combined with excipients;

b. applying a diffusion barrier coating comprising an anionic polymer on said substrate; and

c. applying a coating comprising a hydrophobic material on said diffusion barrier coating.

[0072] In a preferred embodiment the therapeutic agent is applied onto the substrate. Thereafter, the diffusion barrier coating is applied on said substrate over the therapeutic agent. Preferably the diffusion barrier coating is applied until a weight gain, ranging from about 0.1 to 30%, preferably from about 1 to 20%, is reached. Then, the hydrophobic coating is overcoated on the diffusion barrier coating.

[0073] The coatings, including the coating with the therapeutic agent, are preferably applied by means of a film coating process, either in a fluid bed apparatus or in a pan coat, or a atomization process, or alternatively a press coating process.

[0074] In certain preferred embodiments, the coating layers are applied on the substrate by means of a film coating process, by spraying an aqueous polymeric dispersion or an organic or hydro-organic solvent polymeric dispersion with a solid content ranging between 1 and 50% w/w, preferably ranging between 1 and 25%.

[0075] Spheroids comprising the therapeutic agent may also be prepared, for example, by adding a spheronizing agent to the substrate compositions described above prior to or after coating the substrates with the controlled release coating.

[0076] The formulations of the present invention comprise a therapeutically effect amount of the therapeutic agent. In certain preferred embodiments of the present invention, the formulations comprise a plurality of the resultant controlled release substrates to provide a therapeutically effective amount of the therapeutic agent. In certain preferred embodiments, the therapeutic agent is in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

[0077] The final form of the pharmaceutical preparations made in accordance with the invention can vary greatly. Thus, tablets, caplets, capsules, sachets, and the like are contemplated. Tablets, caplets, and capsules are preferred.

[0078] The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

EXAMPLE 1

[0079] In Example 1, naltrexone HCl beads were prepared having the composition listed in Table 1:

TABLE 1

	Ingredients	Amt/unit (mg)	Amt/batch (g)
Step 1. Drug layering	Naltrexone HCl anhydrous	0.658	12.15
	Non-pareil beads (30/35 mesh)	79.788	1473.0
	Opadry Clear (Hydroxypropymethyl cellulose)	0.775	14.73
Step 2. Anionic polymer coat	Eudragit L30D (dry)	3.023	55.8
	Triethyl Citrate	0.756	13.95
	Glyceryl Monostearate	0.284	5.25
Step 3. Controlled release coat	Eudragit RS30D (dry)	32.5	600.0
	Triethyl citrate	6.5	120.0
	Cab-o-sil	1.625	30.0
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	4.062	75.0
Total (on dry basis)		130	2400

Bead Manufacturing Process

1. Dissolve naltrexone HCl and Opadry Clear in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
2. Disperse Eudragit L30D, Triethyl citrate, and glyceryl monostearate in water. Spray the dispersion onto the drug-loaded beads in the fluid bed coater.
3. Disperse Eudragit RS30D, triethyl citrate, and cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
4. Dissolve Opadry Clear in water. Spray the solution onto the beads in the fluid bed coater.
5. Cure the beads at 40°C for 24 hours.

EXAMPLE 2

[0080] In Example 2, Naltrexone HCl beads were prepared as in Example 1 (BHT was added (dissolved) in step 1), having the composition listed in Table 2 below:

TABLE 2

	Ingredients	Amt/unit (mg)	Amt/batch (g)
Step 1. Drug layering	Naltrexone HCl anhydrous	0.658	12.15
	Non-pareil beads (30/35 mesh)	79.788	1473.0
	Opadry Clear (Hydroxypropymethyl cellulose)	0.775	14.31
	BHT	0.029	0.54
Step 2. Anionic polymer coat	Eudragit L30D (dry)	3.023	55.8
	Triethyl Citrate	0.756	13.95
	Glyceryl Monostearate	0.284	5.25
Step 3. Controlled release coat	Eudragit RS30D (dry)	32.5	600.0
	Triethyl citrate	6.5	120.0
	Cabosil	1.625	30.0
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	4.062	75.0
Total (on dry basis)		130.0	2400.0

EXAMPLE 3

[0081] In Example 3, Naltrexone HCl beads were prepared as in Example 1 (ascorbic acid was added (dissolved) in Step 1), having the composition listed in Table 3:

TABLE 3

	Ingredients	Amt/unit (mg)
Step 1. Drug layering	Naltrexone HCl anhydrous	0.584
	Non-pareil beads (30/35 mesh)	80.26
	Opadry Clear (Hydroxypropymethyl cellulose)	0.341
	Ascorbic acid	0.065
Step 2. Anionic polymer coat	Eudragit L30D (dry)	3.023
	Triethyl Citrate	0.756
	Glyceryl Monostearate	0.284
Step 3. Controlled release coat	Eudragit RS30D (dry)	32.5
	Triethyl citrate	6.5
	Cabosil	1.625
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	3.532
	Cab-o-sil	0.531
Total (on dry basis)		130.0

EXAMPLE 4

[0082] In Example 4, Naltrexone HCl beads were prepared as in Example 1 (ascorbic acid and sodium ascorbate were added (dissolved) in step 1), having the composition listed in Table 4 below:

TABLE 4

	Ingredients	Amt/unit (mg)
Step 1. Drug coating	Naltrexone HCl anhydrous	2.00
	Non-pareil beads (30/35 mesh)	39.08
	Opadry Clear (Hydroxypropymethyl cellulose)	2.00
	Sodium ascorbate	0.067
	Ascorbic acid	0.133
Step 2. Diffusion barrier coat	Eudragit L 55	2.164
	Triethyl Citrate	0.433
	Cab-O-Sil	0.108
Step 3. Controlled release coat	Eudragit RS	17.475
	Triethyl citrate	3.495
	Cab-O-Sil	0.874
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cab-O-Sil	0.271
Total		69.998

EXAMPLE 5

[0083] In Example 5, a formulation was prepared as in Example 4 (glycerol monostearate was used in place of cabosil), having the formulation listed in Table 5 below:

TABLE 5

	Ingredients	Amt/unit (mg)
Step 1. Drug coating	Naltrexone HCl anhydrous	2.00
	Non-pareil beads (30/35 mesh)	38.98
	Opadry Clear (Hydroxypropymethyl cellulose)	2.00
	Sodium ascorbate	0.067
	Ascorbic acid	0.133
Step 2. Diffusion barrier coat	Eudragit L 55	2.159
	Triethyl Citrate	0.432
	Glyceryl monostearate	0.216
Step 3. Controlled release coat	Eudragit RS	17.475
	Triethyl citrate	3.495
	Cab-O-Sil	0.874
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cab-O-Sil	0.271
Total		70.001

Example 6

[0084] Oxycodone controlled release beads are prepared according to the following formula and process:

Table 6

Formula Oxycodone HCl beads

	Ingredients	Amt/unit* (mg)
Step 1. Drug layering	Oxycodone HCl	10.5
	Non-pareil beads (30/35 mesh)	45.349
	Opadry Clear	2.5
Step 2. Controlled release coat	Eudragit RS30D (dry)	7.206
	Eudragit RL30D (dry)	0.379
	Triethyl citrate	1.517
	Cabosil	0.379
Step 3. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cabosil	0.271
Total		70.0

Bead Manufacturing Procedure

1. Dissolve oxycodone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
2. Disperse Eudragit RS, Eudragit RL, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
3. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.
4. Cure the beads at 45°C for 24 hours.

Example 7

[0085] Oxycodone controlled release beads with an anionic polymer coating are prepared according to the following formula and process:

Table 7

Formula Oxycodone HCl beads

	Ingredients	Amt/unit* (mg)
Step 1. Drug layering	Oxycodone HCl	10.5
	Non-pareil beads (30/35 mesh)	45.349
	Opadry Clear	2.5
Step 2. Anionic polymer coating	Eudragit L30D (dry)	2.0
	Triethyl citrate	0.4
	Carbosil	0.1
Step 3. Controlled release coat	Eudragit RS30D (dry)	7.206
	Eudragit RL30D (dry)	0.379
	Triethyl citrate	1.517
	Cabosil	0.379
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cabosil	0.271
Total		72.5

Bead Manufacturing Procedure

1. Dissolve oxycodone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
2. Disperse Eudragit L30D, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
3. Disperse Eudragit RS, Eudragit RL, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
4. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.
5. Cure the beads at 45°C for 24 hours.

It would be expected that the dissolution of Example 7 would be slower than the dissolution of Example 6 due to the inclusion of the anionic polymer coating.

Example 8

[0086] In Example 8, naltrexone beads without a diffusion barrier coat were prepared having the composition listed in Table 8 below.

Table 8

	Ingredients	Amt/unit (mg)	Amt/batch (g)
Step1. Drug Layering	Naltrexone HCl anhydrous	1.000	14.00
	Non-pareil beads (30/35 mesh)	47.998	672.00
	Plasdone C-30 (Povidone)	0.500	7.00
	Talc, USP	0.500	7.00
Step 2. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	2.500	35.00
Step 3. Sustained release coat	Eudradit RS30D (dry)	8.814	123.40
	Dibutyl Sebacate	1.764	24.70
	Talc, USP	4.407	61.70
	Tween 80	0.018	0.25
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	2.500	35.00
Total (on dry basis)		70.001	980.05

Bead Manufacturing Process

1. Dissolve naltrexone HCl and Plasdone in water. Disperse the talc in the drug solution. Spray the drug dispersion onto the non-pareil beads in the fluid bed coater with Wurster insert.
2. Dissolve Opadry clear in water. Spray the solution onto the drug loaded beads in the fluid bed coater.
3. Disperse the Eudragit RS30D, Dibutyl Sebacate, Tween 80 and Talc in water. Spray the dispersion onto beads in the fluid bed coater.
4. Dissolve Opadry clear in water. Spray the solution onto beads in the fluid bed coater.

Example 9

[0087] In Example 9, the formulations from Example 8 and Examples 1-5 were dissolution tested using the dissolution method below.

Dissolution Method

1. Apparatus- USP Type II (paddle), 50 rpm at 37°C.
2. Sampling time- 1, 2, 4, 12, 24, and 36 hours (1, 2, 4, 8, and 18 hours for Example 8).
3. Media- 900 ml pH 6.5 phosphate buffer.
4. Analytical method- High performance liquid chromatography.

Dissolution Results for Example 8 are listed in Table 9 below:

Table 9

Time (hrs.)	% Dissolved
1	2.0
2	22.0
4	43.0
8	59.0
18	74.0

Dissolution results for Examples 1-5 are listed in Table 10 below

Table 10

	Example 1	Example 2	Example 3	Example 4	Example 5
Time (hrs.)	% Dissolved	% Dissolved	% Dissolved	% Dissolved	% Dissolved
1	0.0	0.9	0.0	0.4	0.4
2	0.2	4.7	0.0	0.6	0.6
4	0.1	5.1	0.0	0.7	0.8
8	0.4	5.8	0.0	0.8	1.0
12	0.6	8.0	0.2	1.0	1.2
24	1.0	15.2	0.5	1.4	1.5
36	2.3	19.1	1.2	2.2	2.8

[0088] Many other variations of the present invention will be apparent to those skilled in the art and are meant to be within the scope of the claims appended hereto.

What is claimed is:

1. A pharmaceutical formulation comprising:
   a substrate comprising an opioid antagonist;
   a diffusion barrier coating comprising an anionic polymer coated over said substrate; and
   a coating comprising a hydrophobic material coated over said diffusion barrier coating.

2. The pharmaceutical formulation of claim 1, wherein the substrate comprises opioid antagonist coated over a core.

3. The pharmaceutical formulation of claim 2, wherein the core is a pharmaceutically acceptable inert bead.

4. The pharmaceutical formulation of claim 1, wherein the antagonist is dispersed in matrix multiparticulates.

5. The pharmaceutical formulation of claim 1, wherein the opioid antagonist is protonated.

6. The pharmaceutical formulation of claim 5, wherein the protonated opioid antagonist has affinity for the anionic polymer.

7. The pharmaceutical formulation of claim 1, wherein the anionic polymer is selected from the group consisting of an acrylic polymer, acrylic copolymer, methacrylic polymer, methacrylic copolymer, and mixtures thereof.

8. The pharmaceutical formulation of claim 1, wherein the anionic polymer is a non-acrylic enteric coating material.

9. The pharmaceutical formulation of claim 8, wherein the enteric coating material is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate

trimellatate, cellulose acetophthalate, cellulose acetate terephthalate, polyvinyl alcohol phthalate, and mixtures thereof.

10. The pharmaceutical formulation of claim 1, wherein the diffusion barrier coating is in an amount from about 0.1 to about 10 percent by weight of the substrate.

11. The pharmaceutical formulation of claim 1, wherein the opioid antagonist is in a therapeutically effective amount.

12. The pharmaceutical formulation of claim 1, comprising a plurality of said substrates.

13. The pharmaceutical formulation of claim 12, wherein said plurality of said substrates comprises a therapeutically effective amount of said the opioid antagonist.

14. The pharmaceutical formulation of claim 1, wherein the coating comprising the hydrophobic material provides for the controlled release of the opioid antagonist.

15. The pharmaceutical formulation of claim 1, wherein the coating comprising the hydrophobic material provides for the sequestration of the opioid antagonist.

16. The pharmaceutical formulation of claim 1, wherein the hydrophobic material is selected from the group consisting of a cellulosic material, a cellulosic polymer, an acrylic polymer or copolymer, a methacrylic polymer or copolymer, and mixtures thereof.

17. The pharmaceutical formulation of claim 1 wherein said opioid antagonist is selected from the group consisting of naltrexone, naloxone and pharmaceutically acceptable salts thereof.

18. A pharmaceutical formulation comprising:
a substrate comprising an opioid analgesic
a diffusion barrier coating comprising an anionic polymer coated over said substrate; and

a coating comprising a hydrophobic material coated over said diffusion barrier coating; said hydrophobic material providing for the controlled release of the opioid analgesic.

19. The pharmaceutical formulation of claim 18, wherein the substrate comprises the opioid analgesic coated over a core.

20. The pharmaceutical formulation of claim 19, wherein the core is a pharmaceutically acceptable bead.

21. The pharmaceutical formulation of claim 18, wherein the opioid analgesic is dispersed in matrix multiparticulates.

22. The pharmaceutical formulation of claim 18, wherein the opioid analgesic is protonated.

23. The pharmaceutical formulation of claim 22, wherein the protonated opioid analgesic has affinity for the anionic polymer.

24. The pharmaceutical formulation of claim 18, wherein the anionic polymer is selected from the group consisting of an acrylic polymer, arylic copolymer, methacrylic polymer, methacrylic copolymer, and mixtures thereof.

25. The pharmaceutical formulation of claim 18, wherein the anionic polymer is a non-acrylic enteric coating material.

28. The pharmaceutical formulation of claim 25, wherein the enteric coating material is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellatate, cellulose acetophthalate, cellulose acetate terephthalate, polyvinyl alcohol phthalate, and mixtures thereof.

29. The pharmaceutical formulation of claim 18, wherein the diffusion barrier coating is in an amount of from about 0.1 to about 10 percent by weight of the substrate.

30. The pharmaceutical formulation of claim 18, wherein the opioid analgesic is in a therapeutically effective amount.

31. The pharmaceutical formulation of claim 18, comprising a plurality of said substrates.

32. The pharmaceutical formulation of claim 31, wherein said plurality of said substrates comprises a therapeutically effective amount of said opioid analgesic.

33. The pharmaceutical formulation of claim 18, wherein the hydrophobic material is selected from the group consisting of a cellulosic material, a cellulosic polymer, an acrylic polymer or copolymer, a methacrylic polymer or copolymer, and mixtures thereof.

34. The pharmaceutical formulation of claim 18, wherein said opioid analgesic is selected from the group consisting of anileridine, buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, morphine, meperidine, oxycodone, oxymorphone, tramadol, salts thereof, and mixtures thereof.

35. A process for preparing a pharmaceutical formulation comprising:
a) forming a substrate comprising an opioid antagonist;
b) applying a diffusion barrier coating comprising an anionic polymer onto said substrate; and
c) applying a coating comprising a hydrophobic material over said diffusion barrier coating.

36. The process of claim 35, wherein said opioid antagonist is applied onto said substrate.

37. The process of claim 35, wherein the substrate is a pharmaceutically acceptable inert bead.

38. The process of claim 35, wherein the substrate is a matrix multiparticulate.

39. The process of claim 35, wherein the opioid antagonist is protonated.

40. The process of claim 39, wherein the protonated opioid antagonist has affinity for the anionic polymer.

41. The process of claim 35, wherein the anionic polymer is selected from the group consisting of an acrylic polymer, acrylic copolymer, methacrylic polymer, methacrylic copolymer, non-acrylic enteric coating material, and mixtures thereof.

42. The process of claim 35, wherein the diffusion barrier coating is in an amount from about 0.1 to about 20 percent by weight of the substrate.

43. The process of claim 35, wherein the opioid antagonist is present in a therapeutically effective amount.

44. The process of claim 35, wherein said formulation comprises a plurality of said substrates.

45. The process of claim 44, wherein said plurality of said substrates comprises a therapeutically effective amount of said opioid antagonist.

46. The process of claim 35, wherein the coating comprising the hydrophobic material provides for the controlled release of the opioid antagonist.

47. The process of claim 35, wherein the coating comprising the hydrophobic material provides for the sequestration of the opioid antagonist.

48. The pharmaceutical formulation of claims 35 wherein said opioid antagonist is selected from the group consisting of naltrexone, naloxone or pharmaceutically acceptable salts thereof.

49. The process of claim 35, wherein the hydrophobic material is selected from the group consisting of a cellulosic material, a cellulosic polymer, an acrylic polymer or copolymer, a methacrylic polymer or copolymer, and mixtures thereof.

50. A process for preparing a pharmaceutical formulation comprising:
a) forming a substrate comprising an opioid analgesic;

b) applying a diffusion barrier coating comprising an anionic polymer onto said substrate; and

c) applying a coating comprising a hydrophobic material over said diffusion barrier coating said coating providing for the controlled release of the opioid analgesic.

51. The process of claim 50, wherein said opioid analgesic is selected from the group consisting of anileridine, buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, morphine, meperidine, oxycodone, oxymorphone, tramadol, salts thereof and mixtures thereof.

52. A method of treating pain in a patient in need of said treatment comprising administering the formulation of claim 18 to said patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/25601

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14, 9/16
US CL : 424/489, 490

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/489, 490

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,436,438 B1 (MOMBERGER et al) 20 August 2002 (20.08.2002), column 3, lines 10-15, column 6, lines 39-51.	1-25, 28-52

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
14 November 2003 (14.11.2003)

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/25601

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 26 and 27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
These claims are not cited.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.